Open Access

Original Article

Diagnostic Accuracy of Anti-Mullerian Hormone for Polycystic Ovary Syndrome

Kulsoom Bahadur, Aamir Ijaz, Shehla Baqai*, Naveed Asif**

Rehman Medical Institute, Peshawar Pakistan, *Combined Military Hospital, Lahore/National University of Medical Sciences (NUMS) Pakistan, **Combined Military Hospital, Quetta/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To determine the diagnostic accuracy of Anti-Mullerian Hormone in Polycystic ovary syndrome detection, keeping Rotterdam criteria as a gold standard.

Study Design: Cross-sectional study.

Place and Duration of Study: Armed Forces Institute of Pathology, Rawalpindi and Rehman Medical Institute, (RMI) Peshawar, Pakistan from Jul 2018 to Jun 2019.

Methodology: The study included one hundred and forty clinically suspected patients of polycystic ovary syndrome (PCOS) of 16-45 years of age. Blood samples were analyzed for serum Anti-Mullerian Hormone analysis on Architect ci 8200 System using the Chemiluminescent immunoassay technique. AMH was considered positive for Polycystic ovary syndrome at a threshold of 4.9ng/ml. In addition, AMH's diagnostic accuracy was evaluated, considering the Rotterdam criteria of PCOS as a gold standard.

Results: The mean age and mean BMI of the study subjects were 26.73±5.07 years and 30.43±4.83kg/m^2, respectively. The mean follicle-stimulating and Luteinizing hormones were 4.34±0.68mIU/ml and 5.24±1.43mIU/ml, respectively. The mean Anti-Mullerian hormone of all patients was 7.79±4.62ng/ml. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), the likelihood ratio of a positive test (LR+) and Likelihood ratio of a Negative Test (LR-) of Anti-Mullerian hormone were 91.8%, 74.7%, 73.7%, 92.2%, 3.63%, 0.11%, respectively and overall diagnostic accuracy was 82.1%.

Conclusion: Anti-Mullerian hormone can effectively determine the existence of Polycystic ovary syndrome among women of reproductive age and serve as a sensitive diagnostic tool for Polycystic ovary syndrome.

Keywords: Anti-mullerian hormone, Disorders of endocrine, Hyperandrogenism, Polycystic ovary syndrome (PCOS), Rotterdam criteria.

How to Cite This Article: *Bahadur K, Ijaz A, Baqai S, Asif N. Diagnostic Accuracy of Anti-Mullerian Hormone for Polycystic Ovary Syndrome. Pak Armed Forces Med J 2023; 73(2): 329-332. DOI: https://doi.org/10.51253/pafmj.v73i2.4249*

INTRODUCTION

Polycystic ovary syndrome (PCOS) is characterized by ovulatory dysfunction, hyperan-drogenism and ovarian morphological characteristics.[1] PCOS is closely related to insulin resistance, in which multiple body functions are compromised, resulting in several health issues, including menstrual dysfunction, hirsutism, acne, obesity, and metabolic syndrome.[2,3] In 2003, a consensus workshop led by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) in Rotterdam suggested that if any 2 out of 3 requirements were met, PCOS would be present in the absence of other entities that could be responsible for this findings.[4] As stated by the Rotterdam criteria, out of three characteristics, at least two characteristics must be present to label as PCOS. These characteristics are; chronic oligo-ovulation/ anovulation, hyperandro genism (clinical or bio-chemical), detection of polycystic ovaries on ultra-sound and exclusion of other etiologies such as congenital adrenal hyperplasia, androgen-secreting tumours, Cushing syndrome, thyroid dysfunction and hyperprolactinaemia.[5]

Anti-Müllerian hormone (AMH), the transforming growth factor (TGF)-β, controls follicle production. This hormone prevents the development of primordial follicles by reducing follicles' responsiveness to follicle-stimulating hormone (FSH), resulting in the pooling of small antral follicles.[6] Unbalanced secretion of Anti-Müllerian Hormone (AMH) by maturing follicles in ovaries has been reported in PCOS.[7] High serum AMH levels in females with PCOS presumably lead to significant anovulation and correlate with pathogenesis and pathophysiological features, including changes in intra-ovarian or extra-ovarian variables like LH, FSH, testosterone and estrogen. AMH triggers follicular atresia, which can often correspond to the follicle pattern of females with PCOS.[8] In PCOS women, increased levels of AMH are consistent with hyperandrogenism and lower rates of live births.[9] However, the lack of an internationally accepted guideline for serum AMH measurement and

Correspondence: Dr Aamir Ijaz, Department of Chemical Pathology, Bahria International Hospital, Rawalpindi-Pakistan

Received: 04 May 2020; revision received: 16 Aug 2020; accepted: 29 Oct 2020

the inability to define thresholds/cut-off values makes it more challenging to use serum AMH concentration to diagnose PCOS.[10]

There is limited local literature on the role of AMH in diagnosing PCOS. Therefore, the current study aims to determine the accuracy of AMH in diagnosing PCOS among reproductive age group women suspected of PCOS.

METHODOLOGY

The cross-sectional study at the Armed Forces Institute of Pathology Rawalpindi and Rehman Medical Institute (RMI), Peshawar, Pakistam, from July 2018 to June 2019. The sample size was calculated after considering the anticipated prevalence of PCOS as 19.5%, based on Rotterdam criteria. Institutional Review Board/Ethics Review Committee, Rehman Medical Institute, Peshawar (RMI/RMI-REC/Approval 59) approved the study.

Inclusion Criteria: Women aged 16-45 years suspected of PCOS due to the presence of one or more features of PCOS were included in the study.

Exclusion Criteria: Women with chronic kidney disease (creatinine>1.5mg/dl), diabetes mellitus, cardiac or respiratory disorders, and in whom one ovary was removed due to some complication like ectopic pregnancy or large ovarian cyst were excluded from the study.

After taking informed consent, detailed history was taken. All the patients were evaluated by Rotterdam criteria (at least two features, chronic oligo-ovulation and/or anovulation, clinical and/or biochemical evidence of hyperandrogenism, polycystic ovaries on imaging). Demographic details like name, age, BMI, and marital status were noted. Patients with clinical and biochemical features suggestive of were evaluated by Rotterdam criteria for PCOS.

Blood specimens were taken and analyzed in the laboratory for assessment of serum AMH on Architect ci 8200 System using the Chemiluminescent immunoassay technique irrespective of any specific day of the menstrual cycle. All the standard operating procedures were followed while taking blood specimens and Serum AMH analysis. Patients were divided into two groups based on Rotterdam criteria PCOS positive and PCOS Negative. Serum AMH levels, i.e., positive (>4.9ng/ml) and negative (<4.9ng/ml), were assessed in these two groups.[11]

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Quantitative variables were expressed as mean±SD and qualitative variables were expressed as frequency and percentages. A contingency table was generated to calculate sensitivity, specificity, PPV, NPV, LR+, LR- and diagnostic accuracy with 95% confidence intervals. The receiver operating characteristics (ROC) curve was used to determine the validity of the serum AMH test to differentiate PCOS from non-PCOS in clinically suspected patients based on an area under the curve (AUC) of 0.80 or more.

RESULTS

The mean age and mean BMI of the study subjects were 26.73±5.07years and 30.43±4.83kg/m^2, respectively. The mean systolic blood pressure was 134.57 ±10.12mmHg, the mean diastolic blood pressure was 83.25±6.51mmHg, and the mean waist circum-ference was 104.53±8.79cm. Hirsutism was present in 122 (87.1%) patients, while acne was in 58(41.4%). The mean FSH, LH, testosterone and estradiol were 4.34 ±0.68mIU/ml, 5.24±1.43mIU/ml, 5.18±1.34nmol/l and 65.04±14.54pg/ml, respectively. The mean AMH was were7.79±4.62ng/ml (Table-I).

Table -I: Baseline Parameters of the patients (n=140)

Parameters	n(%)
Age (years)	26.73±5.07
Body mass index kg/m^2	30.43±4.83
Blood pressure systolic (mmHg)	134.57±10.12
Blood pressure diastolic (mmHg)	83.25±6.51
Hip circumference (cm)	104.53±8.79
Follicle stimulating hormone (mIU/ml)	4.34±0.68
Luteinizing hormone (mIU/ml)	5.24±1.43
Testosterone (nmol/l)	5.18±1.34
Estradiol (pg/ml)	65.04±14.54
Anti-Mullerian Hormone (ng/ml)	7.79±4.62
Parameters	n(%)
Hirsutism	122 (87.1%)
Acne	58 (41.4%)

The area under the curve (AUC) shown by the ROC curve of AMH for predicting PCOS was found to be 0.913 in the study subjects (Figure).

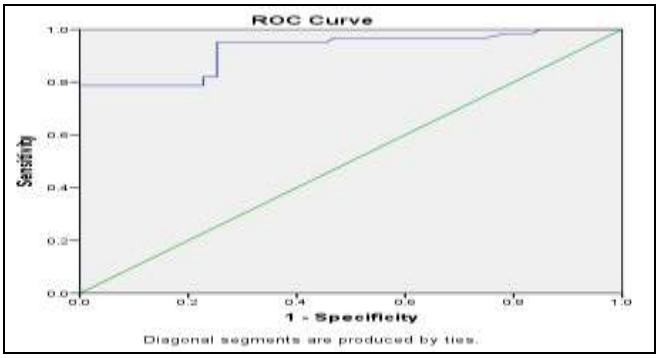

Figure: ROC showing prediction of Polycystic ovary syndrome based on Anti-Mullerian Hormone level (AUC = 0.91)

The contingency table for AMH in patients suspected of PCOS is shown in Table-II.

Table-II: Contingency Table for Anti-Mullerian Hormone in the patient with suspected Polycystic Ovary Syndrome (n-140)

		Polycystic Ovary Syndrome	
		Positive	Negative
Anti-Mullerian Hormone	Positive (≥4.56)	56(40%)	20(14.3%)
	Negative (<4.56)	5(3.6%)	59(42.1%)

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), the likelihood ratio of a positive test (LR+) and Likelihood ratio of a Negative Test (LR-) of AMH were 91.8%, 74.7%, 73.7%, 92.2%, 3.63%, 0.11% respectively and overall diagnostic accuracy was 82.1% (Table-III).

Table-III: Various parameters of Diagnostic Accuracy of Anti-Mullerian hormone in Polycystic ovary syndrome (n=140)

Diagnostic Accuracy Parameters	Value	95% Confidence Interval
Sensitivity	91.8%	81.9% to 97.2%
Specificity	74.7%	63.6% to 83.8%
Positive predictive value	73.7%	65.5% to 80.4%
Negative predictive value	92.2%	83.4% to 96.5%
Likely hood ratio+	3.63%	2.4 to 5.34
Likely hood ratio-	0.11%	0.05 to 0.26
Overall Diagnostic Accuracy	82.1%	74.7% to 88.1%

DISCUSSION

PCOS is a serious and medically heterogeneous multifactorial disorder considered a major cause of androgen excess in females of the reproductive age group. It is associated with type II diabetes, obesity and associated complications, e.g., metabolic syndrome and cardiovascular diseases, and increased risk of endometrial and breast cancer.[11,12] PCOS can be detected by ultrasound, free androgen levels (or index) and LH: FSH ratio. AMH has been estimated in previous studies to determine its diagnostic accuracy in different grades of PCOS.[13,14]

A local cohort study found that PCOS patients had significantly higher levels of Body mass index, Luteinizing Hormone (LH), LH: FSH ratio, androstenedione, testosterone, insulin and prolactin than the control group.[15] High AMH levels in PCOS patients are also related to an increased risk of preterm delivery.[15]

In our study, the AMH cut-off value was 4.9ng/ml. AMH was highly sensitive (91.8%) and moderately specific (74.7%) for PCOS, with an overall diagnostic accuracy of 82.1% with AUC=0.91 and an AMH cut-off value of 4.9ng/ml. A meta-analysis demonstrated the sensitivity and specificity of 79.4% and 82.8%, respectively, in detecting PCOS in symptomatic females with AMH cut-off value >4.7ng/ml while AUC was 0.87(95% CI; 0.83-0.92), similar to the area under the curve, i.e. 0.87 for the cumulative. ROC curve involving ten different trials.[16] Given the strong association of AMH with PCOS, AMH concentration can be utilized as a biomarker of PCOS detection. Dewailly *et al.*(2011) observed that with AMH ≥4.9-ng/mL, a sensitivity of 92% and specificity of 97% can be achieved, which is better than antral follicle count to discriminate PCOS among females of reproductive age group.[17] Although one very recent meta-analysis has proposed that AMH≥4.7 ng/mL achieved the sensitivity and specificity of 82.8% and 79.4%, respectively, for the diagnosis of PCOS, with AUC of 0.87, there is presently no general and consensual diagnostic threshold of serum AMH for diagnosis of PCOS.[18] Another study constructed a ROC curve showing AUC 0.634 with 95% CI (0.5–0.798).[19] European Society of Human Reproduction and Embryology guidelines (2018) do not recommend estimating serum AMH concentration as substitute for detecting polycystic ovarian morphology or as a single test product for detecting PCOS.[20]

AMH can accurately diagnose PCOS in women of reproductive age and function as a non-interventional biomarker for PCOS. Thus, instead of using multiple criteria, we can consider performing an AMH test to screen PCOS. Further studies are, however, required to establish this marker.

CONCLUSION

Anti-Mullerian hormone can effectively determine the existence of Polycystic ovary syndrome among women of reproductive age and serve as a sensitive diagnostic tool for Polycystic ovary syndrome.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

KB: Data acquisition, data analysis, approval of the final version to be published.

A: Conception, study design, data interpretation, approval of the final version to be published.

SB:, NA: Critical review, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. McCartney CR, Marshall JC. Clinical Practice. Polycystic Ovary Syndrome. N Engl J Med 2016; 375(1): 54-64. doi: 10.1056/NEJMcp1514916.
2. Geisthövel F, Rabe T. The ESHRE/ASRM consensus on polycystic ovary syndrome (PCOS)--an extended critical analysis. Reprod Biomed Online 2007; 14(4): 522-535. doi: 10.1016/s1472-6483(10)60902-9.
3. Macut D, Pfeifer M, Yildiz BO, Diamanti-Kandarakis E. Polycystic ovary syndrome: Novel insights into causes and therapy,Volume:40. Basel: Karger; 2013, [Internet] available at: https://www.karger.com/Article/Pdf/342244.
4. Jalilian A, Kiani F, Sayehmiri F, Sayehmiri K, Khodaee Z, Akbari M, et al. Prevalence of polycystic ovary syndrome and its associated complications in Iranian women: A meta-analysis. Iran J Reprod Med 2015; 13(10): 591-604.
5. Bothou A, Koutlaki N, Iatrakis G, Mastorakos G, Tsikouras P, Liberis V, et al. Antimüllerian Hormone As Indicator Of Ovarian Dysfunction. Acta Endocrinol (Buchar) 2017; 13(2): 237-245.
6. Wiweko B, Handayani LK, Harzif AK, Pratama G, Muharam R, Hestiantoro A, et al. Correlation of anti-Müllerian hormone levels with metabolic syndrome events in polycystic ovary syndrome: A cross-sectional study. Int J Reprod Biomed 2020; 18(3): 187-192. doi: 10.18502/ijrm.v18i3.6716.
7. Dumont A, Robin G, Catteau-Jonard S, Dewailly D. Role of Anti-Müllerian Hormone in pathophysiology, diagnosis and treatment of Polycystic Ovary Syndrome: a review. Reprod Biol Endocrinol 2015; 13: 137. doi: 10.1186/s12958-015-0134-9.
8. Qi X, Pang Y, Qiao J. The role of anti-Müllerian hormone in the pathogenesis and pathophysiological characteristics of polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2016; 199: 82-87. doi: 10.1016/j.ejogrb.2016.01.029.
9. Han X, McShane M, Sahertian R, White C, Ledger W. Pre-mixing serum samples with assay buffer is a prerequisite for reproducible anti-Mullerian hormone measurement using the Beckman Coulter Gen II assay. Hum Reprod 2014; 29(5): 1042-1108. doi: 10.1093/humrep/deu050.
10. Tal R, Seifer CM, Khanimov M, Seifer DB, Tal O. High serum Antimullerian hormone levels are associated with lower live birth rates in women with polycystic ovarian syndrome undergoing assisted reproductive technology. Reprod Biol Endocrinol 2020; 18(1): 20. doi:10.1186/s12958-020-00581-4.
11. Georgescu C. Polycystic Ovary Syndrome Endocrine and Cardio-Metabolic Abnormalities: how to Manage? Acta Endocrinologica (Bucharest) 2015; 11: 77-84. doi: 10.4183/aeb.2015.77
12. Köninger A, Koch L, Edimiris P, Enekwe A, Nagarajah J, Kasimir-Bauer S, et al. Anti-Mullerian Hormone: an indicator for the severity of polycystic ovarian syndrome. Arch Gynecol Obstet 2014; 290(5): 1023-1030. doi: 10.1007/s00404-014-3317-2.
13. Lie Fong S, Visser JA, Welt CK, de Rijke YB, Eijkemans MJ, Broekmans FJ, et al. Serum anti-müllerian hormone levels in healthy females: a nomogram ranging from infancy to adulthood. J Clin Endocrinol Metab 2012; 97(12): 4650-4655. doi: 10.1210/jc.2012-1440.
14. Sahmay S, Aydin Y, Oncul M, Senturk LM. Diagnosis of Polycystic Ovary Syndrome: AMH in combination with clinical symptoms. J Assist Reprod Gen 2014; 31(2): 213-220.
15. Akram M, Roohi N. Endocrine correlates of polycystic ovary syndrome in Pakistani women. J Coll Physicians Surg Pak 2015; 25(1): 22-26.
16. Hu KL, Liu FT, Xu H, Li R, Qiao J. High antimüllerian hormone levels are associated with preterm delivery in patients with polycystic ovary syndrome. Fertil Steril 2020; 113(2): 444-452.e1. doi: 10.1016/j.fertnstert.2019.09.039.
17. Dewailly D, Gronier H, Poncelet E, Robin G, Leroy M, Pigny P, et al. Diagnosis of polycystic ovary syndrome (PCOS): revisiting the threshold values of follicle count on ultrasound and of the serum AMH level for the definition of polycystic ovaries. Hum Reprod 2011; 26(11): 3123-3139. doi: 10.1093/humrep/der297.
18. Iliodromiti S, Kelsey TW, Anderson RA, Nelson SM. Can anti-Mullerian hormone predict the diagnosis of polycystic ovary syndrome? A systematic review and meta-analysis of extracted data. J Clin Endocrinol Metab 2013; 98(8): 3332-3340. doi: 10.1210/jc.2013-1393.
19. Victoria M, Labrosse J, Krief F, Cédrin-Durnerin I, Comtet M, Grynberg M. Anti Müllerian Hormone: More than a biomarker of female reproductive function. J Gynecol Obstet Hum Reprod 2019; 48(1): 19-24. doi: 10.1016/j.jogoh.2018.10.015.
20. Bakeer E, Radwan R, Mandoury A, Rahman AA, Gad M, Maksoud SA, et al. Anti-Müllerian Hormone as a Diagnostic Marker in Egyptian Infertile Polycystic Ovary Syndrome Females: Correlations with Vitamin D, Total Testosterone, Dyslipidemia and Anthropometric Parameters. J Med Biochem 2018; 37(4): 448-455. doi: 10.1515/jomb-2017-0068.